PATENT SPECIFICATION

NO DRAWINGS

893,209

Date of Application and filing Complete Specification: Nov. 12, 1958.

No. 36393/58.

Application made in United States of America on Nov. 20, 1957.

Complete Specification Published: April 4, 1962.

Index at acceptance:—Class 2(3), U(2:3), U4(A2:B1:B2:C4:C5:X), U7.

International Classification:—C07c.

COMPLETE SPECIFICATION

Production of Steroid Compounds

We, MERCK & CO., INC., a corporation duly organised and existing under the laws of the State of New Jersey, United States of America, of Rahway, New Jersey, United States of America, do hereby declare the

terised. These tertiary amine salts are valuable because of their high degree of anti-inflammatory activity and low incidence of side reactions. As a result of their water solubility these salts are superior to previously known products as anti-inflammatory active ingredients in ophthalmic solutions. They are also superior in ointments for topical application. The amine salts are

PATENTS ACT 1949

SPECIFICATION NO. 893,209

In accordance with the Decision of the Superintending Examiner, acting for the Comptroller-General, dated 24 April 1970, this Specification has been amended unde Section 33 in the following manner:-

Page 1, lines 50 and 55, page 6, lines 99 and 104, *after* "11" *delete* "-oxygenated" *insert* "(- keto or β- hydroxy)-"

Page 2, line 88, *after* "which" *delete* "is alka-" *insert* comma

Page 2, *delete* line 89 *insert* "when diluted"

Page 2, line 90, *after* "water" *delete* full stop *insert* ", is alkaline to conventional indicators whose colour changes at a pH of about 7".

Page 3, lines 68 and 71, *for* "anion" *read* "cation"

Page 5, line 64, *for* "an anion" *read* "a cation"

Page 5, line 95, *after* "805,828" *insert* "and to patent No. 902254"

Page 5, line 118, page 6, lines 14, 21 and 22, *delete* "lower" *insert* "C_{1-5}"

Page 6, *delete* lines "24 to 31"

Page 6, *for* claims "7 and 8" *read* "6 and 7"

THE PATENT OFFICE
8 July 1970

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and thus improves both the yield and purity of the desired product.

The solvent for carrying out the reaction is preferably one in which the steroid phos-

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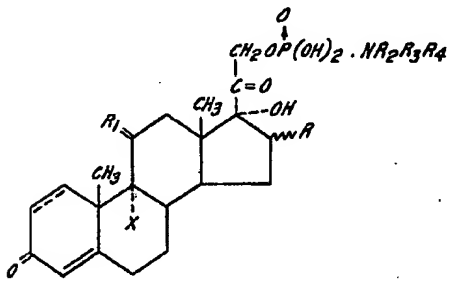
COMPLETE SPECIFICATION

Production of Steroid Compounds

We, MERCK & Co., INC., a corporation duly organised and existing under the laws of the State of New Jersey, United States of America, of Rahway, New Jersey, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention is concerned with processes for producing steroid phosphates having anti-inflammatory activity.

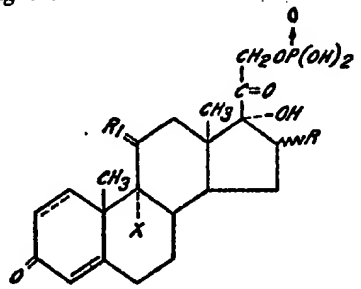
The tertiary lower alkyl amine salts of steroid phosphates having the general formula



can be prepared by the processes of the invention.

In the above formula R_1 is β-hydroxyl or oxo, R_2, R_3, and R_4 are C_{1-5} alkyl radicals, X is a hydrogen or fluorine atom, R is a hydrogen atom or an alkyl group, and the dotted line in the 1(2) position indicates that this linkage is a single or double bond.

The steroid phosphate tertiary amine salts are water-soluble, stable crystalline compounds. Unlike the steroid phosphate free acids and the amorphous alkalimetal salts, the tertiary amine salts are easily characterised. These tertiary amine salts are valuable because of their high degree of anti-inflammatory activity and low incidence of side reactions. As a result of their water solubility these salts are superior to previously known products as anti-inflammatory active ingredients in ophthalmic solutions. They are also superior in ointments for topical application. The amine salts are also useful as intermediates in the preparation of pure steroid dihydrogen phosphates having the formula:



in which R, R_1, and X and the dotted line in the 1(2)-position have the above significance, which also have cortisone-like anti-inflammatory activity.

According to this invention 21-phosphate tertiary lower alkyl amine salts of 3,20-diketo - 17α,21 - dihydroxy - 11 - oxygenated steroids of the 4-pregnene and 1,4-pregnadiene series are prepared by reacting a 21-iodo, 21-bromo, 21-chloro or 21-hydrocarbon sulphonyloxy derivative of a 3,20 - diketo-17α,21 - dihydroxy - 11 - oxygenated steroids of the 4-pregnene and 1,4-pregnadiene series with a tertiary lower alkyl amine phosphate or with a tertiary lower alkyl amine and phosphoric acid, in an alkaline organic solvent medium. The use of an alkaline reaction medium suppresses the formation of the side products by rearrangement of the ketol side chain of the steroid, which is prone to take place in an acidic medium, and thus improves both the yield and purity of the desired product.

The solvent for carrying out the reaction is preferably one in which the steroid phos-

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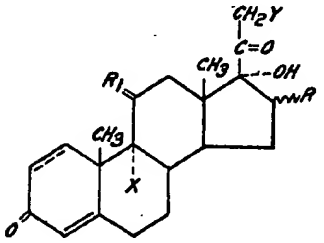
phate tertiary amine salt product is insoluble and the other reaction products and reagents are soluble. This makes it easy to recover the product by conventional means. Acetonitrile has been found to be an excellent solvent fulfilling these qualifications. Other solvents which may be used include the lower aliphatic alcohols such as methanol and tertiary butyl alcohol.

The steroid starting material is a 21-halo compound, i.e. a 21-iodo-, 21-bromo-, or 21-chloro compound, or a 21-methanesulphonate, or a 21-toluenesulphonate, corresponding to the desired product. The starting material has a general formula of:



where X, R, R_1 and the dotted line in the 1(2) position are as previously defined and Y is chlorine, bromine, iodine, or a hydrocarbon sulphonic acid ester group such as methane sulphonyloxy ($-OSO_2CH_3$) or *p*-toluenesulphonyloxy ($-OSO_2C_6H_4CH_4$).

Typical starting compounds are:

21 - iodo - $\Delta^{1,4}$ - pregnadiene - 11β,17α-diol - 3,20 - dione,

21 - bromo - $\Delta^{1,4}$ - pregnadiene - 11β,17α-diol - 3,20 - dione,

21 - chloro - $\Delta^{1,4}$ - pregnadiene - 11β,17α-diol - 3,20 - dione,

$\Delta^{1,4}$ - pregnadiene - 11β,17α,21 - triol - 3,20-dione - 21 - methanesulphonate,

$\Delta^{1,4}$ - pregnadiene - 11β,17α,21 - triol - 3,20-dione - 21 - *p* - toluenesulphonate,

21 - iodo - Δ^4 - pregnene - 11β,17α - diol-3,20 - dione,

9α - fluoro - 21 - iodo - Δ^4 - pregnene-11β,17α-diol - 3,20 - dione,

9α - fluoro - 21 - iodo - $\Delta^{1,4}$ - pregnadiene-11β,16α,17α - triol - 3,20 - dione,

16α - methyl - Δ^4 - pregnene - 11β,17α,21-triol - 3,20 - dione - 21 - methanesulphonate,

21 - iodo - Δ^4 - pregnene - 17α - ol - 3,11,20-trione,

21 - iodo - $\Delta^{1,4}$ - pregnadiene - 17α - ol-3,11,20 - trione,

$\Delta^{1,4}$ - pregnadiene - 17α,21 - diol - 3,11,20-trione - 21 - methanesulphonate, and

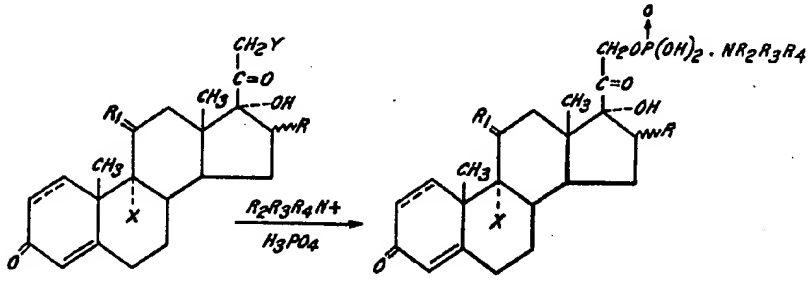
$\Delta^{1,4}$ - pregnadiene - 17α,21 - diol - 3,11,20-trione - 21 - *p* - toluenesulphonate.

Other steroid starting materials will also be evident.

Phosphoric acid and a tertiary lower alkyl amine are the other reagents in the process of this invention. The phosphoric acid reagents may be of commercial concentration, e.g. 85% or 100%, or of somewhat lower concentration.

The amine reagent is a tertiary lower alkyl amine such as trimethylamine, triethylamine, tributylamine, diethyl isopropylamine, methyl ethyl isopropylamine or triisoamylamine.

The steroid starting material is reacted simultaneously with phosphoric acid and the amine in a process which proceeds according to the following equation:



where R, R_1, R_2, R_3, R_4, X, Y, and the dotted line in the 1(2)-position are as previously defined.

Both the phosphoric acid and the amine reagent—or the amine phosphate if this is used—are preferably present in excess based on the quantity of steroid. This excess may range from slight to substantial. For example, the amount of phosphoric acid may be as much as ten times the stoichiometric quantity. The mole ratio of amine to phosphoric acid is preferably about 2:1, but may be varied, as long as an alkaline reaction medium is maintained. By "alkaline" is meant a reaction medium which is alkaline to conventional indicators when diluted with water. Since both amine and phosphoric acid are present, the reaction is in effect between the steroid starting material and an amine phosphate salt. In fact, the amine can be neutralized with phosphoric acid prior to contact with the steroid starting

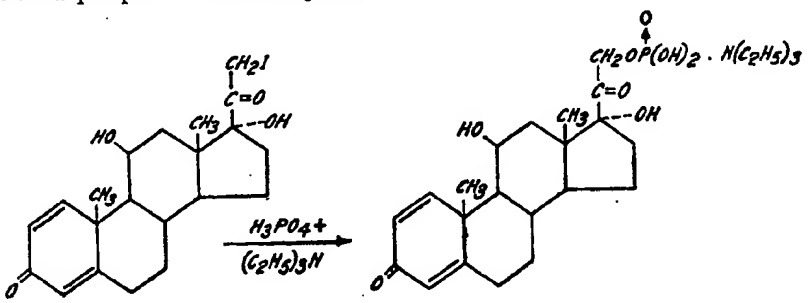
material, and the resulting salt, which in the preferred embodiment is the diamine phosphate, reacted with the steroid reagent.

A small amount of silver phosphate may be present in the reaction medium, although it is not essential. Silver phosphate appears to catalyse the reaction.

The reaction temperature is not critical, although, in general, elevated temperatures are preferred. The reaction proceeds readily at reflux temperature. The reaction time likewise is not critical and may vary from about one hour to ten hours or more. The reaction time is of course dependent on temperature, the lower temperatures necessitating longer reaction times.

The steroid phosphate amine salt product may be precipitated by concentration of the organic solvent, followed by cooling of the concentrate to about room temperature or lower. The product may then be recovered by conventional means such as filtration. The other constituents of the reaction mixture remain in solution, so that separation of a product of high purity is effected.

A preferred embodiment of the present invention is the production of prednisolone-21-dihydrogen phosphate triethylamine salt. In the preferred mode of operation, 21-iodo - $\Delta^{1,4}$ - pregnadiene - 11β,17α - diol-3,20 - dione is reacted with triethylamine and phosphoric acid according to the equation:



An excess of phosphoric acid based on the amount of steroid is present, as previously explained; and the preferred mole ratio of triethylamine to phosphoric acid is 2:1. Instead of 21 - iodo - $\Delta^{1,4}$ - pregnadiene - 11β,17α - diol - 3,20 - dione, the starting material may be 21 - bromo - $\Delta^{1,4}$-pregnadiene - 11β,17α - diol - 3,20 - dione, 21 - chloro - $\Delta^{1,4}$ - pregnadiene - 11β,17α-diol - 3,20 - dione, or $\Delta^{1,4}$ - pregnadiene-11β,17α,21 - triol - 3,20 - dione-21-methanesulphonate.

The steroid phosphate amine salts produced according to the present invention have cortisone-like anti-inflammatory activity with a minimum of side effects. They may be dissolved in aqueous solutions for ophthalmic use. The compounds produced in accordance with the present invention, being water-soluble, cause no irritation to the eye as may the water-insoluble steroids used heretofore in ophthalmic preparations. The novel compounds of this invention may also be incorporated in ointments for topical application.

The steroid phosphate amine salts prepared according to this invention are also easily converted to the corresponding steroid dihydrogen phosphate free acids and alkali metal salts thereof. The conversion to the dihydrogen phosphate is most readily effected by contact of a solution of the steroid phosphate amine salt in a suitable solvent such as methanol, with a strongly acidic anion-exchange resin in its hydrogen form, and eluting the resulting system. Among the suitable anion-exchange resins are polystyrene resins cross-linked with divinyl benzene having the exchangeable hydrogen atoms in the form of sulfonic acid groups. An example of such a resin is that sold under the registered trade mark "Amberlite IR-120" by Rohm & Haas Company, Philadelphia, Pennsylvania. The resulting steroid dihydrogen phosphate, which is a 21-dihydrogen phosphate ester of a Δ^4-pregnene compound such as cortisone or hydrocortisone or a $\Delta^{1,4}$-pregnadiene such as prednisone or prednisolone, is a water-soluble compound suitable for ophthalmic preparations or in solutions for either oral or intravenous administration where rapid response is required. The 21-dihydrogen phosphate may be converted to a salt by treating the above eluate with sodium hydroxide.

This invention will now be further described with reference to specific embodiments thereof.

EXAMPLE 1

A solution of 102 cc. of triethylamine and 24 cc. of phosphoric acid in 144 cc. of acetonitrile was poured into a suspension of 48 g. of 21 - iodo - $\Delta^{1,4}$ - pregnadiene-11β,17α - diol - 3,20 - dione and 6 g. of silver phosphate in 360 cc. of acetonitrile. The mixture was boiled at reflux for about 90 minutes with a clear solution resulting after about 20 minutes. The solution was

filtered hot to remove trace insolubles and the filtrate concentrated under reduced pressure at a bath temperature of 50° C. to a volume of 120 cc. The concentrate was aged for 16 hours at 25° C. and the resulting slurry was diluted with 120 cc. of acetonitrile, aged at 0° to 5° C. for one hour and filtered. The filter cake of $\Delta^{1,4}$-pregnadiene - 11β,17α,21 - triol - 3,20-dione - 21 - hydrogen phosphate triethylamine salt was washed with acetonitrile and ether and dried in air at 25° C. Yield 33.7 to 34.8 g. (61% to 63%); dec. 201° C.; E% 268 at 2,470 Å. Analysis showed the triethylamine content to be 19.2% (theoretical: 18.7%). Electrophoresis showed a single spot.

EXAMPLE 2

The procedure of Example 1 was repeated except that the silver phosphate was omitted. The same product was obtained as in Example 1.

EXAMPLE 3

To a slurry of 3.72 g. of $\Delta^{1,4}$ - pregnadiene-11β,17α,21 - triol - 3,20 - dione-21-methanesulphonate in 30 cc. of acetonitrile was added a solution of 8.5 cc. of triethylamine and 2 cc. of 85% phosphoric acid in 12 cc. of acetonitrile. The mixture was boiled under reflux for three hours, concentrated under reduced pressure to about 10 cc., diluted with about 50 cc. of absolute ethanol, reconcentrated to about 10 cc., and allowed to stand until crystallization was complete. The mixture was diluted with 8 cc. of acetonitrile, filtered, and the product, $\Delta^{1,4}$-pregnadiene - 11β,17α,21 - triol - 3,20 - dione-21 - hydrogen phosphate triethylamine salt, washed with ether. Yield 1.7 g. (37%); m.p. 200°—201.5° C. E% 269 at 2,470 Å.

EXAMPLE 4

To a slurry of 4 g. of 21 - iodo - Δ^4-pregnene - 11β,17α - diol - 3,20 - dione, 6.4 g. of silver phosphate and 3.2 g. of a diatomaceous earth filter aid and 30 cc. of acetonitrile was added a solution of 8.4 cc. of triethylamine and 2 cc. of 85% phosphoric acid in 12 cc. of acetonitrile. The mixture was heated at 50° to 55° C. for seven hours and filtered, and the filtrate was concentrated under reduced pressure to about 10 cc. The residue was diluted with ca. 50 cc. of absolute ethanol, reconcentrated to about 10 cc., and allowed to stand until crystallization was complete. The mixture was diluted with 8 cc of acetonitrile, cooled, and washed with ether. The product obtained was Δ^4 - pregnene - 11β,17α,21 - triol-3,20 - dione - 21 - hydrogen phosphate triethylamine salt. Yield, 1.94 g. (42.4%); m.p. 183° to 187°; E% 298 at 2,470 Å.

EXAMPLE 5

To a slurry of 4 g. of 21 - iodo - Δ^4-pregnene - 11β,17α - diol - 3,20 - dione, 6.4 g. of silver phosphate and 3.2 g. of diatomaceous earth filter aid in 30 ml. of tertiary butyl alcohol was added a slurry of 8.5 ml. of triethylamine and 2.0 ml. of 85% phosphoric acid in 22 ml. of tertiary butyl alcohol. The mixture was boiled under reflux for three hours, filtered, and the filtrate concentrated under reduced pressure to about 10 ml. The residue was diluted with *ca.* 50 cc. of absolute ethanol, reconcentrated to about 10 cc., and allowed to stand until crystallization was complete. The mixture was diluted with 7 ml. of acetonitrile and the product was washed with ether. Electrophoresis of the product gave one spot having the same mobility as a known sample of Δ^4 - pregnene - 11β,17α, 21 - triol - 3,20 - dione - 21 - hydrogen phosphate triethylamine salt. M.p. 175°—180° C.; E% 298 at 2,480 Å.

EXAMPLE 6

To a slurry of 4.0 g. of 21 - iodo - Δ^4-pregnene - 11β,17α - diol - 3,20 - dione and 0.5 g. of silver phosphate and 22 ml. of acetonitrile was added a mixture of 14.35 ml. of tri - *n* - butylamine, 2.2 ml. of 85% phosphoric acid and 20 ml. of acetonitrile. The mixture was boiled under reflux for three hours and filtered, and the filtrate was concentrated under reduced pressure to a small volume. The residue was triturated with absolute ethanol and filtered. The filtrate was concentrated under reduced pressure. The residue was identified as $\Delta^{1,4}$-pregnadiene - 11β,17α,21-triol-3,20-dione-21 - hydrogen phosphate tri - *n* - butylamine salt by electrophoresis.

EXAMPLE 7

To a slurry of 4.0 g. of 21 - iodo - Δ^4-pregnene - 17α - ol - 3,11,20 - trione and 0.5 g. of silver phosphate and 30 ml. of acetonitrile was added a solution of 8.5 ml. of triethylamine and 2.0 ml. of 85% phosphoric acid in 12 ml. of acetonitrile. The mixture was boiled under reflux for three hours and filtered, and the filtrate was concentrated under reduced pressure to a small volume. The residue was triturated with methanol and filtered. The filtrate was concentrated under reduced pressure to a small volume. The residue was identified as Δ^4-pregnene - 17α,21 - diol - 3,11,20 - dione-21 - hydrogen phosphate triethylamine salt by electrophoresis.

EXAMPLE 8

To a slurry of 1.6 g. of 21 - chloro - $\Delta^{1,4}$-pregnadiene - 11β,17α - diol - 3,20 - dione, 3.2 g. of silver phosphate, and 1.6 g. of diatomaceous earth filter aid in 11 ml. of acetonitrile was added a solution of 4.3 ml. of triethylamine and 1.0 ml. of 85% phosphoric acid in 10 ml. of acetonitrile. The mixture was boiled under reflux for six hours and filtered, and the filtrate was concentrated under reduced pressure to about 5 ml. The resulting slurry was diluted with

5 ml. of acetonitrile and allowed to stand until crystalization wals complete. The mixture was filtered and the product washed with acetonitrile and ether. The product was $\Delta^{1,4}$ - pregnadiene - 11β,17α,21 - triol-3,20 - dione - 21 - hydrogen phosphate triethyl amine salt. Yield 0.73 g. (31.7%); m.p. 199°—201° C.; E%279 at 2,470 Å.

EXAMPLE 9

To a slurry of 4 g. of 21 - iodo - Δ^4-pregnene - 11β,17α - diol - 3,20 - dione and 3.2 g. of diatomaceous earth filter aid and 30 cc. of acetonitrile was added a solution of 8.4 cc. of triethylamine and 2 cc. of 85% phosphoric acid in 12 cc. of acetonitrile. The mixture was heated at reflux for six hours, filtered, and the filtrate concentrated under reduced pressure to about 10 cc. The residue was flushed with absolute ethanol and allowed to stand until crystallization was complete. The mixture was diluted with 8 cc. of acetonitrile, cooled, and the product washed with ether. The resulting product was Δ^4 - pregnene - 11β,17α,21 - triol - 3,20-dione - 21 - hydrogen phosphate triethylamine salt. Yield 1.33 g. (29%); m.p. 184°—188° C.

EXAMPLE 10

To a slurry of 2.33 g. of Δ^4 - pregnene-11β,17α,21 - triol - 3,20 - dione - 21 - *p*-toluenesulphonate in 12 cc. of acetonitrile was added a solution of 4.2 cc. of triethylamine and 1 cc. of 85% phosphoric acid in 10 cc. of acetonitrile. The solution that resulted was allowed to stand at room temperature for six hours, boiled under reflux for one hour, and concentrated to a syrup under reduced pressure. The syrup was allowed to stand for six days, during which time Δ^4 - pregnene - 11β,17α,21 - triol - 3,20-dione - 21 - hydrogen phosphate triethylamine salt crystallized. The slurry was diluted with 3.5 cc. of acetonitrile, allowed to stand 24 hours at room temperature, cooled at 0°—5° C. for one hour, filtered, and the product washed with ether. Yield, 0.58 g. (25%).

The amine salts of steroid phosphates obtained according to the present invention can be converted to either the corresponding acid phosphate ester or its sodium salt as has been previously indicated. The following example describes a specific procedure for this type of reaction with reference to th conversion of $\Delta^{1,4}$ - pregnadiene - 11β, 17α,21 - triol - 3,20 - dione - 21 - hydrogen phosphate triethylamine salt to $\Delta^{1,4}$ - pregnadiene - 11β,17α,21 - triol - 3,20 - dione-21 - dihydrogen phosphate monosodium salt.

EXAMPLE 11

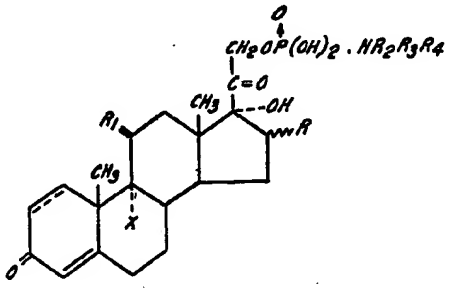
A solution of 20 g. of $\Delta^{1,4}$ - pregnadiene-11β,17α,21 - triol - 3,20 - dione - 21 - hydrogen phosphate triethylamine salt in 100 cc. of methanol was passed over an anion exchange resin column containing 38.4 cc. of "Amberlite IR-120" resin in its hydrogen form over a period of 90 minutes. The column was eluted with 200 cc. of methanol. The eluate showed a constant slight spot with an ultraviolet scanner when elution was complete. The eluate was neutralized by the addition of a solution of 1.6 g. of sodium hydroxide in 160 cc. of methanol. The neutralized solution had a pH of 5.7 as determined by pH indicator paper, or about 6.7 for a 50% aqueous methanol solution as determined by a pH meter. The neutralized solution was concentrated under reduced pressure at a temperature below 35° C. to a volume of 140 cc. From precipitation of Δ^4 - pregnene - 17β,21 - diol-3,11,20 - trione - 21 - hydrogen phosphate monosodium salt was observed. This salt was precipitated by the slow addition of 600 cc. of absolute ether at 25° C. The product was filtered and washed with ether and dried in air at 25° C. Yield 17.2 to 17.6 g. (95% to 97%); moisture (Karl Fischer's method) 5.5%; E% 312 to 314 at 2,470 Å. Analysis revealed a trace (0.18%) of dry ethylamine. Electrophoresis showed a single spot.

In view of the provisions of Section 9 of the Patents Acts 1949—61, attention is directed to our prior patent No. 805,828.

WHAT WE CLAIM IS:—

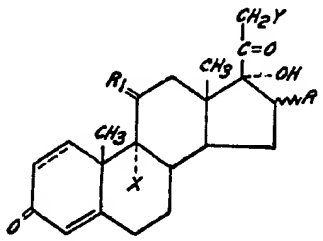
1. A process for preparing 21-phosphate tertiary lower alkyl amine salts of 3,20-diketo - 17α,21 - dihydroxy - 11 - oxygenated steroids of the 4-pregnene and1,4-pregnadiene series, which comprises reacting a 21-iodo, 21-bromo, 21-chloro-, or 21-hydrocarbon sulphonyloxy derivative of a 3,20-diketo - 17α,21 - dihydroxy - 11 - oxygenated steroid of the 4 - pregnene or 1,4 - pregnadiene series with a tertiary C_{1-5} alkyl amine phosphate, or with a tertiary C_{1-5} alkylamine and phosphoric acid, in an alkaline organic solvent medium.

2. A process for producing tertiary lower alkyl amine salts of unsaturated pregnane-21-dihydrogen phosphate esters having the general formula:



where R_1 is H or O=, R_2, R_3, and R_4 are lower radicals, X is a hydrogen or

fluorine atom, R is a hydrogen atom or an alkyl group, and the dotted line in the 1(2) position indicates that this linkage is a single or double bond, which comprises combining a compound having the general formula:



where Y is chlorine, bromine, iodine, or a hydrocarbon sulphonyloxy group, with a tertiary C_{1-5} alkyl amine phosphate, or with a tertiary C_{1-5} alkyl amine and phosphoric acid, in an alkaline organic solvent medium.

3. The process of Claim 2, in which the tertiary lower alkylamine is triethylamine.

4. A process claimed in any one of Claims 1—3, in which the 21-substituent is a methanesulphonyloxy or *p*-toluenesulphonyloxy group.

5. A process as claimed in any of the preceding claims in which an excess of the tertiary lower alkyl amine phosphate, or of the tertiary lower alkyl amine and of phosphoric acid, is used.

6. A process according to any one of the preceding claims including the step of converting the product to the 21-dihydrogen phosphate salt thereof by passing the product over a strongly acidic anion exchange resin in its hydrogen form, eluting the resulting system and adding sodium hydroxide to the eluate.

7. A process as claimed in Claim 1, substantially as hereinbefore described with reference to any one of of Examples 1—10.

8. Amine phosphate steroid salts, when prepared by a process as claimed in any preceding claim or an obvious chemical equivalent of such a process.

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